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DATE: Wednesday, February 15, 2006

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		<i>DB=PGPB,USPT,USOC,EPAB,JPAB,DWPI,TDBD; THES=ASSIGNEE; PLUR=YES; OP=AND</i>	
<input type="checkbox"/>	L1	anti-CD70	12
<input type="checkbox"/>	L2	L1 and conjugate	6
<input type="checkbox"/>	L3	L1 and (toxin or toxoid or cytotoxin)	4
<input type="checkbox"/>	L4	ki24 or Ki-24	6
<input type="checkbox"/>	L5	L4 and (toxin or toxoid or cytotoxin or apoptosis)	1

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<input type="checkbox"/>	L2	L1 and Cd70	561
<input type="checkbox"/>	L3	@py<=2002	31333042
<input type="checkbox"/>	L4	L3 and L2	123
<input type="checkbox"/>	L5	L4 and (toxin or toxoid or cytotoxin or apoptosis)	123
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<input type="checkbox"/>	L6	20020077458 or 6433147 or 6455040 or 20020150534 or 20020106735 or 6358508	23
<input type="checkbox"/>	L7	L6 and L3	6

END OF SEARCH HISTORY

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=> s cd70 or cd27L or cd27lg or ki24 or ki-24 or anti-cd70

L1 1932 CD70 OR CD27L OR CD27LG OR KI24 OR KI-24 OR ANTI-CD70

=> s toxoid or toxin or cytotoxin or apoptosis or "cell death"

L2 1360872 TOXOID OR TOXIN OR CYTOTOXIN OR APOPTOSIS OR "CELL DEATH"

=> s L1 and L2

L3 839 L1 AND L2

=> dup remove

ENTER L# LIST OR (END):l3

PROCESSING COMPLETED FOR L3

L4 762 DUP REMOVE L3 (77 DUPLICATES REMOVED)

=> s L4 and py<=2002

4 FILES SEARCHED...

L5 513 L4 AND PY<=2002

=> s calicheamicin or LLE33288 or LL-E33288

L6 2709 CALICHEAMICIN OR LLE33288 OR LL-E33288

=> s L5 and L6

L7 4 L5 AND L6

=> dis L7 1-4 bib

L7 ANSWER 1 OF 4 PCTFULL COPYRIGHT 2006 Univentio on STN

AN 2002083921 PCTFULL ED 20021107 EW 200243

TIEN NULEIC ACIDS AND CORRESPONDING PROTEINS USEFUL IN THE DETECTION AND

TREATMENT OF VARIOUS CANCERS

TIFR ACIDES NUCLEIQUES ET PROTEINES CORRESPONDANTES UTILES POUR LA DETECTION

ET LE TRAITEMENT DE DIVERS CANCERS

IN JAKOBOVITS, Aya, 3135 Hutton Drive, Beverly Hills, CA 90210, US;

CHALLITA-EID, Pia, M., 15745 Morrison Street, Encino, CA 91436, US;

FARIS, Mary, 2538 Almaden Court, Los Angeles, CA 90077, US;

GE, Wangmao, Apt. #314, 4838 Hollow Corner Road, Culver City, CA 90230,

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HUBERT, Rene, S., 1644 No. Occidental Boulevard, Los Angeles, CA 90026,

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MORRISON, Robert, Kendall, 1044 Yale Street, Santa Monica, CA 90403, US;

RAITANO, Arthur, B., 10807 Cushdon Avenue, Los Angeles, CA 90064, US

AGENSYS, INC., 1545 17th Street, Santa Monica, CA 90404, US [US, US]

MURASHIGE, Kate, H., Morrison & Foerster LLP, Suite 500, 3811 Valley

Centre Drive, San Diego, CA 92130-2332, US

LAF English

LA English

DT Patent
PI ****WO 2002083921 A2 20021024***
DS W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU
CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN
IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN
MW MX MZ NO NZ OM PH PL PT RO RU SD SE SG SI SK SL TJ TM
TN TR TT TZ UA UG UZ VN YU ZA ZM ZW
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RW (EPO): AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE TR
RW (OAPI): BF BJ CF CG CI CM GA GN GQ GW ML MR NE SN TD TG
AI WO 2002-US11654 A 20020410
PRAI US 2001-60/283,112 20010410
US 2001-60/282,739 20010410
US 2001-60/286,630 20010425

L7 ANSWER 2 OF 4 PCTFULL COPYRIGHT 2006 Univentio on STN
AN 2002029032 PCTFULL ED 20020627 EW 200215
TIEN WHOLE CELL ENGINEERING BY MUTAGENIZING A SUBSTANTIAL PORTION OF A
TIFR STARTING GENOME, COMBINING MUTATIONS, AND OPTIONALLY REPEATING
MANIPULATION DE CELLULE ENTIERE PAR MUTAGENESE D'UNE PARTIE
SUBSTANTIELLE D'UN GENOME DE DEPART, PAR COMBINAISON DE MUTATIONS ET
EVENTUELLEMENT PAR REPETITION
IN SHORT, Jay, M., P.O. Box 7214, Rancho Santa Fe, CA 92067-7214, US [US,
US];
FU, Pengcheng, 7588 Charmant Drive #1914, San Diego, CA 92122-5079, US
[AU, US];
LATTERICH, Martin, 12539 Motellano Terrace, San Diego, CA 92130, US [DE,
US];
WEI, Jing, 10725 Wexford St. #6, San Diego, CA 92131, US [CN, US];
LEVIN, Michael, 7565 Tupelo Cove, San Diego, CA 92126, US [RU, US]
PA DIVERSA CORPORATION, 4955 Directors Place, San Diego, CA 92121, US [US,
US], for all designates States except US;
SHORT, Jay, M., P.O. Box 7214, Rancho Santa Fe, CA 92067-7214, US [US,
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FU, Pengcheng, 7588 Charmant Drive #1914, San Diego, CA 92122-5079, US
[AU, US], for US only;
LATTERICH, Martin, 12539 Motellano Terrace, San Diego, CA 92130, US [DE,
US], for US only;
WEI, Jing, 10725 Wexford St. #6, San Diego, CA 92131, US [CN, US], for
US only;
LEVIN, Michael, 7565 Tupelo Cove, San Diego, CA 92126, US [RU, US], for
US only
AG EINHORN, Gregory, P., Fish & Richardson P.C., 4350 La Jolla Village
Drive, San Diego, CA 92122, US
LAF English
LA English
DT Patent
PI ****WO 2002029032 A2 20020411***
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MW MX MZ NO NZ PH PL PT RO RU SD SE SG SI SK SL TJ TM TR
TT TZ UA UG US UZ VN YU ZA ZW
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RW (EAPO): AM AZ BY KG KZ MD RU TJ TM
RW (EPO): AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE TR
RW (OAPI): BF BJ CF CG CI CM GA GN GQ GW ML MR NE SN TD TG
AI WO 2001-US31004 A 20011001
PRAI US 2000-09/677,584 20000930
US 2001-60/279,702 20010328
US 2001-PCT/US01/19367 20010614

L7 ANSWER 3 OF 4 PCTFULL COPYRIGHT 2006 Univentio on STN
AN 2002018620 PCTFULL ED 20020705 EW 200210
TIEN NEUTROKINE-ALPHA AND NEUTROKINE-ALPHA SPLICE VARIANT
TIFR NEUTROKINE-ALPHA ET VARIANT D'EPISSAGE DE NEUTROKINE-ALPHA
IN YU, Guo-Liang, 242 Gravatt Drive, Berkeley, CA 94705, US [US, US];
EBNER, Reinhard, 9906 Shelburne Terrace #316, Gaithersburg, MD 20878, US
[DE, US];
NI, Jian, 17815 Fair Lady Way, Germantown, MD 20874, US [CN, US];
ROSEN, Craig, A., 22400 Rolling Hill Lane, Laytonsville, MD 20882, US
[US, US];
ULLRICH, Stephen, 4713 Rams Head Court, Rockville, MD 20853, US [US, US]
PA HUMAN GENOME SCIENCES, INC., 9410 Key West Avenue, Rockville, MD 20850,

US [US, US], for all designates States except US;
YU, Guo-Liang, 242 Gravatt Drive, Berkeley, CA 94705, US [US, US], for
US only;
EBNER, Reinhard, 9906 Shelburne Terrace #316, Gaithersburg, MD 20878, US
[DE, US], for US only;
NI, Jian, 17815 Fair Lady Way, Germantown, MD 20874, US [CN, US], for US
only;
ROSEN, Craig, A., 22400 Rolling Hill Lane, Laytonsville, MD 20882, US
[US, US], for US only;
ULLRICH, Stephen, 4713 Rams Head Court, Rockville, MD 20853, US [US,
US], for US only

AG HOOVER, Kenley, 9410 Key West Avenue, Rockville, MD 20850, US
LAF English
LA English
DT Patent

PI ***WO 2002018620 A2 20020307***
DS W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU
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AI WO 2001-US25549 A 20010815
PRAI US 2000-60/225,628 20000815
US 2000-60/227,008 20000823
US 2000-60/234,338 20000922
US 2000-60/240,806 20001017
US 2000-60/250,020 20001130
US 2001-60/276,248 20010306
US 2001-60/293,499 20010525
US 2001-60/296,122 20010607
US 2001-60/304,809 20010713

L7 ANSWER 4 OF 4 PCTFULL COPYRIGHT 2006 Univentio on STN
AN 2001096551 PCTFULL ED 20020826
TIEN WHOLE CELL ENGINEERING BY MUTAGENIZING A SUBSTANTIAL PORTION OF A
STARTING GENOME, COMBINING MUTATIONS, AND OPTIONALLY REPEATING
TIFR INGENIERIE CELLULAIRE COMPLETE PAR MUTAGENESE D'UNE PARTIE SUBSTANTIELLE
D'UN GENOME DE DEPART, PAR COMBINAISON DE MUTATIONS ET EVENTUELLEMENT
REPETITION
IN SHORT, Jay, M.
PA DIVERSA CORPORATION;
SHORT, Jay, M.
DT Patent

PI ***WO 2001096551 A2 20011220***
DS W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU
CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN
IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN
MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT
TZ UA UG US UZ VN YU ZA ZW GH GM KE LS MW MZ SD SL SZ TZ
UG ZW AM AZ BY KG KZ MD RU TJ TM AT BE CH CY DE DK ES FI
FR GB GR IE IT LU MC NL PT SE TR BF BJ CF CG CI CM GA GN
GW ML MR NE SN TD TG
AI WO 2001-US19367 A 20010614
PRAI US 2000-09/594,459 20000614
US 2000-09/677,584 20000930

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COST IN U.S. DOLLARS	SINCE FILE	TOTAL
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FULL ESTIMATED COST	47.95	48.16

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FILE CONTAINS CURRENT INFORMATION.
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L7 ANSWER 1 OF 4 PCTFULL COPYRIGHT 2006 Univentio on STN
 PI ****WO 2002083921 A2 20021024***

DETD . . . maytansinoids, yttrium-4 bismuth, ricin, ricin A-chain, doxorubicin, daunorubicin, taxol, ethidium bromide, mitomycin, etoposide, teniposide, vincristine, vinblastine, colchicine, dihydroxy anthracin dione, actinomycin, diphtheria ****toxin***, Pseudomonas exotoxin (PE) A, PE40, abrin, abrin A chain, modeccin A chain, alpha-sarcin, gelonin, mitogellin, retstrictocin, p4enomycin, enomycin, curicin, croton, ****calicheamicin***, saponaria officinalis inhibitor, and glucocorticoid and other chemotherapeutic agents, as well as radioisotope's such as At211, V31, V251 Y90, Re186

Immunol. 12:923, 1994 and Eldridge, J. H. et al., Sem. Hematol. 30:16, 1993). ****Toxin*** -targeted delivery technologies, also known as receptor mediated targeting, such as those of Avant Immunotherapeutics, Inc.

. . . or immunization of the peptides of the invention, eg. adeno and adeno-associated virus vectors, retroviral vectors, Salmonella typhi vectors, detoxified anthrax ****toxin*** vectors, and the like, will be apparent to those skilled in the art from the description herein.

. . . of Figure 2 proteins are useful to systemically treat cancers that express a protein of Figure 2, either as conjugates with a ****toxin*** or therapeutic agent, or as naked antibodies capable of inhibiting cell proliferation or function.

. . . the invention, inhibition of ligand binding or signal transduction pathways, modulation of tumor cell differentiation, alteration of tumor angiogenesis factor profiles, and/or ****apoptosis***.

11: 117-127). Some therapeutic approaches involve conjugation of naked antibody to a ****toxin*** or radioisotope, such as the conjugation of Y or I... to anti-CD20 antibodies (e.g., ZevalinTM, IDEC Pharmaceuticals Corp. or BexxarTM Coulter Pharmaceuticals),. . . of the invention can be administered in conjunction with radiation, chemotherapy or hormone ablation. Also, antibodies can be conjugated to a ****toxin*** such as ****calicheamicin*** (e.g., MylotargTM, Wyeth-Ayerst, Madison, NJ, a recombinant humanized IgG4 - kappa antibody conjugated to antitumor antibiotic ****calicheamicin***) or a maytansinoid (e.g., taxane-based Tumor-Activated Prodrug, TAP, platform-4 ImmunoGen, Cambridge, MA, also see e.g., US Patent 5,416,064).

. . . mAbs act include: inhibition of cell growth, modulation of cellular differentiation, modulation of tumor angiogenesis factor profiles, and the induction of ****apoptosis***. The mechanism(s) by which a particular mAbs of the invention exert an anti-tumor effect is evaluated using any number of in vitro assays that evaluate ****cell*** ****death*** such as ADCC, ADMMC, complement-mediated cell lysis, and so forth, as is generally known in the art.

. . . vaccines of the invention are well known in the art, and include, e.g., thyroglobulin, albumins such as human serum albumin, tetanus ****toxoid***, polyanionic acids such as poly L-lysine, poly L-glutamic acid, influenza, hepatitis B virus core protein, and the like. The vaccines can. . . .

. . . class II molecules. Examples of such amino acid bind many HLA Class II molecules include sequences from antigens such as tetanus ****toxoid*** at positions 830-843 (QYIKANSKFIGITE; SEQ ID NO.

In vivo assays that evaluate the promotion of ***apoptosis*** are useful in evaluating therapeutic compositions.

those that specifically bind epitopes of a protein of the invention exposed on the cell surface and thus are useful in targeting mAb- ***toxin*** conjugates. Immunogens for generation of such mAbs include those designed to encode, or contain an entire protein of the invention, regions.

The genes in Figure 2 also play a role in cell cycle modulation and ***apoptosis***. Parental cells and cells expressing the gene of interest are compared for differences in cell cycle regulation using a well-established BrdU assay.

are analyzed for entry into the G1, S, and G2M phases of the cell cycle. Alternatively, the effect of stress on

apoptosis is evaluated in control parental cells and cells expressing the gene of interest, including normal and tumor prostate, colon and lung. various chemotherapeutic agents, such as etoposide, flutamide, etc, and protein synthesis inhibitors, such as cycloheximide. Cells are stained with annexin V-FITC and ***cell*** ***death*** is measured by FACS analysis. The modulation of ***cell*** ***death*** by genes of Figure 2 play a critical role in regulating tumor progression and tumor load.

a genes set for in Figure 2, and/or its respective gene product, plays a role in cell growth, transformation, invasion or ***apoptosis***, it is used as a target for diagnostic, prognostic, preventative and therapeutic purposes.

S-S RKRK HN 24
254 I RV VV AV F F TCFL Py 24
277 F SH LD RL L D ESAQ ***KI*** ***24***
45 L PV L Y LI I F V ASI LL 23
517
TABLE XXIII - 154P2A8 HLA-
DRB1*0101 15 - mers
POS 1 2.

=> dis his

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L1 1932 S CD70 OR CD27L OR CD27LG OR KI24 OR KI-24 OR ANTI-CD70
L2 1360872 S TOXOID OR TOXIN OR CYTOTOXIN OR APOPTOSIS OR "CELL DEATH"
L3 839 S L1 AND L2
L4 762 DUP REMOVE L3 (77 DUPLICATES REMOVED)
L5 513 S L4 AND PY<=2002
L6 2709 S CALICHEAMICIN OR LLE33288 OR LL-E33288
L7 4 S L5 AND L6

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FILE 'PCTFULL' ENTERED AT 16:34:24 ON 15 FEB 2006

FILE 'STNGUIDE' ENTERED AT 16:34:50 ON 15 FEB 2006

=> s L5 and CD27

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=> s L3 and CD27

0 CD70
0 CD27L
0 CD27LG
0 KI24

```

0 KI
6 24
0 KI-24
    (KI (W) 24)
0 ANTI
0 CD70
0 ANTI-CD70
    (ANTI (W) CD70)
0 TOXOID
0 TOXIN
0 CYTOTOXIN
0 APOPTOSIS
15 "CELL"
0 "DEATH"
0 "CELL DEATH"
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0 CD27
L8 0 L3 AND CD27

=> s L1

0 CD70
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0 CD27LG
0 KI24
0 KI
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L9 0 CD70 OR CD27L OR CD27LG OR KI24 OR KI-24 OR ANTI-CD70

=> FIL MEDLINE BIOSIS EMBASE CAPLUS TOXCENTER CANCERLIT DISSABS PCTFULL
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specify a corrected file name or you can enter "IGNORE" to continue
accessing the remaining file names entered.
ENTER A FILE NAME OR (IGNORE):ignore
COST IN U.S. DOLLARS                               SINCE FILE          TOTAL
                                                    ENTRY          SESSION
FULL ESTIMATED COST                               0.24             50.67

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FILE 'BIOSIS' ENTERED AT 16:37:02 ON 15 FEB 2006
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=> dis his

(FILE 'HOME' ENTERED AT 16:25:49 ON 15 FEB 2006)

FILE 'MEDLINE, BIOSIS, EMBASE, CAPLUS, TOXCENTER, DISSABS, PCTFULL'
ENTERED AT 16:26:14 ON 15 FEB 2006
L1 1932 S CD70 OR CD27L OR CD27LG OR KI24 OR KI-24 OR ANTI-CD70
L2 1360872 S TOXOID OR TOXIN OR CYTOTOXIN OR APOPTOSIS OR "CELL DEATH"

```


L3 839 S L1 AND L2
L4 762 DUP REMOVE L3 (77 DUPLICATES REMOVED)
L5 513 S L4 AND PY<=2002
L6 2709 S CALICHEAMICIN OR LLE33288 OR LL-E33288
L7 4 S L5 AND L6

FILE 'STNGUIDE' ENTERED AT 16:31:31 ON 15 FEB 2006

FILE 'PCTFULL' ENTERED AT 16:34:24 ON 15 FEB 2006

FILE 'STNGUIDE' ENTERED AT 16:34:50 ON 15 FEB 2006

L8 0 S L3 AND CD27
L9 0 S L1

FILE 'MEDLINE, BIOSIS, EMBASE, CAPLUS, TOXCENTER, DISSABS, PCTFULL'
ENTERED AT 16:37:02 ON 15 FEB 2006

=> s L5 and CD27
L10 439 L5 AND CD27

=> s L5 and ki24
L11 3 L5 AND KI24

=> dis L11 1-3 bib

L11 ANSWER 1 OF 3 PCTFULL COPYRIGHT 2006 Univentio on STN
AN 2002094999 PCTFULL ED 20021210 EW 200248
TIEN POLYNUCLEOTIDE ENCODING A NOVEL TRP CHANNEL FAMILY MEMBER, TRP-PLIK2,
AND SPLICE VARIANTS THEREOF
TIFR POLYNUCLEOTIDE CODANT UN NOUVEAU MEMBRE DE LA FAMILLE DES CANAUX TRP,
TRP-PLIK2, ET VARIANT D'EPISSAGE DE CE POLYNUCLEOTIDE
IN LEE, Ning, 926 Rhoads Drive, Belle Mead, NJ 08807, US [US, US];
CHEN, Jian, 121 York Drive, Princeton, NJ 08540, US [CN, US];
FEDER, John, 277 Dutchtown Zion Road, Belle Mead, NJ 08502, US [US, US];
WU, Shujian, 972 Ithan Lande, Langhorne, PA 19047, US [CN, US];
CHANG, Han, 2 Ann's Court, Princeton Junction, NJ 08550, US [US, US];
LEE, Liana, 8 Petunia Drive Apt. 1J, North Brunswick, NJ 08902, US [US,
US];
BLANAR, Michael, 1325 Summerhill Drive, Malvern, PA 19355, US [CA, US];
BOL, David, 1467 Franklin Road, Langhorne, PA 19047, US [US, US]
PA BRISTOL-MYERS SQUIBB COMPANY, P.O. Box 4000, Route 206 and Provinceline
Road, Princeton, NJ 08543-4000, US [US, US], for all designates States
except US;
LEE, Ning, 926 Rhoads Drive, Belle Mead, NJ 08807, US [US, US], for US
only;
CHEN, Jian, 121 York Drive, Princeton, NJ 08540, US [CN, US], for US
only;
FEDER, John, 277 Dutchtown Zion Road, Belle Mead, NJ 08502, US [US, US],
for US only;
WU, Shujian, 972 Ithan Lande, Langhorne, PA 19047, US [CN, US], for US
only;
CHANG, Han, 2 Ann's Court, Princeton Junction, NJ 08550, US [US, US],
for US only;
LEE, Liana, 8 Petunia Drive Apt. 1J, North Brunswick, NJ 08902, US [US,
US], for US only;
BLANAR, Michael, 1325 Summerhill Drive, Malvern, PA 19355, US [CA, US],
for US only;
BOL, David, 1467 Franklin Road, Langhorne, PA 19047, US [US, US], for US
only
AG D'AMICO, Stephen, Bristol-Myers Squibb Company, P.O. Box 4000, Route 206
and Provinceline Road, Princeton, NJ 08543-4000, US
LAF English
LA English
DT Patent
PI ***WO 2002094999 A2 20021128***
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RW (OAPI): BF BJ CF CG CI CM GA GN GQ GW ML MR NE SN TD TG
AI WO 2002-US16164 A 20020522

PRAI US 2001-60/292,599 20010522
US 2002-60/362,944 20020308

L11 ANSWER 2 OF 3 PCTFULL COPYRIGHT 2006 Univentio on STN
AN 2002074959 PCTFULL ED 20021010 EW 200239
TIEN A NOVEL HUMAN LEUCINE-RICH REPEAT CONTAINING PROTEIN EXPRESSED
PREDOMINATELY IN NERVOUS SYSTEM TISSUES, HLRNS1
TIFR HLRNS1: NOUVELLE PROTEINE HUMAINE A REPETITIONS RICHES EN LEUCINE
EXPRIMEE ESSENTIELLEMENT DANS DES TISSUS DU SYSTEME NERVEUX
IN RAMANATHAN, Chandra, 41 Alison Avenue, Wallingford, CT 06492, US;
FEDER, John, 277 Dutchtown Zion Road, Belle Mead, NJ 08502, US;
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AG D'AMICO, Stephen, Bristol-Myers Squibb Company, P.O. Box 4000, Route 206
and Provinceline Road, Princeton, NJ 08543-4000, US
LAF English
LA English
DT Patent
PI ***WO 2002074959 A2 20020926***
DS W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU
CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN
IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN
MW MX MZ NO NZ PH PL PT RO RU SD SE SG SI SK SL TJ TM TR
TT TZ UA UG UZ VN YU ZA ZW
RW (ARIPO): GH GM KE LS MW MZ SD SL SZ TZ UG ZW
RW (EAPO): AM AZ BY KG KZ MD RU TJ TM
RW (EPO): AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE TR
RW (OAPI): BF BJ CF CG CI CM GA GN GQ GW ML MR NE SN TD TG
AI WO 2001-US50457 A 20011220
PRAI US 2001-60/259,479 20010103
US 2001-60/260,616 20010109

L11 ANSWER 3 OF 3 PCTFULL COPYRIGHT 2006 Univentio on STN
AN 2002044210 PCTFULL ED 20020624 EW 200223
TIEN NOVEL HUMAN NUCLEIC ACID MOLECULES AND POLYPEPTIDES ENCODING A NOVEL
HUMAN ION CHANNEL EXPRESSED IN SPINAL CORD AND BRAIN
TIFR NOUVELLES MOLECULES D'ACIDE NUCLEIQUE HUMAIN ET POLYPEPTIDES CODANT POUR
UN NOUVEAU CANAL IONIQUE HUMAIN EXPRIME DANS LA MOELLE EPINIERE ET DANS
LE CERVEAU
IN GAUGHAN, Glen, 30 Mansfield Drive #1503, Northford, CT 06472, US;
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NELSON, Thomas, 12 Azalea Court, Lawrenceville, NJ 08648, US;
PA MINTIER, Gabe, 318 Morrison Ave., Hightstown, NJ 08520, US;
RAMANATHAN, Chandra, 41 Alison Avenue, Wallingford, CT 06492, US
BRISTOL-MYERS SQUIBB COMPANY, P.O. Box 4000, Route 206 and Provinceline
Road, Princeton, NJ 08543-4000, US [US, US]
AG D'AMICO, Stephen, Bristol-Myers Squibb Company, P.O. Box 4000, Route 206
and Provinceline Road, Princeton, NJ 08543-4000, US
LAF English
LA English
DT Patent
PI ***WO 2002044210 A2 20020606***
DS W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU
CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN
IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN
MW MX MZ NO NZ PH PL PT RO RU SD SE SG SI SK SL TJ TM TR
TT TZ UA UG UZ VN YU ZA ZW
RW (ARIPO): GH GM KE LS MW MZ SD SL SZ TZ UG ZM ZW
RW (EAPO): AM AZ BY KG KZ MD RU TJ TM
RW (EPO): AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE TR
RW (OAPI): BF BJ CF CG CI CM GA GN GQ GW ML MR NE SN TD TG
AI WO 2001-US45336 A 20011130
PRAI US 2000-60/250,587 20001201

=> FIL STNGUIDE
COST IN U.S. DOLLARS
FULL ESTIMATED COST

SINCE FILE
ENTRY
11.67
TOTAL
SESSION
62.34

FILE 'STNGUIDE' ENTERED AT 16:38:26 ON 15 FEB 2006
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FILE CONTAINS CURRENT INFORMATION.
LAST RELOADED: Feb 10, 2006 (20060210/UP).

=> dis his

(FILE 'HOME' ENTERED AT 16:25:49 ON 15 FEB 2006)

FILE 'MEDLINE, BIOSIS, EMBASE, CAPLUS, TOXCENTER, DISSABS, PCTFULL'
ENTERED AT 16:26:14 ON 15 FEB 2006

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L1      1932 S CD70 OR CD27L OR CD27LG OR KI24 OR KI-24 OR ANTI-CD70
L2      1360872 S TOXOID OR TOXIN OR CYTOTOXIN OR APOPTOSIS OR "CELL DEATH"
L3      839 S L1 AND L2
L4      762 DUP REMOVE L3 (77 DUPLICATES REMOVED)
L5      513 S L4 AND PY<=2002
L6      2709 S CALICHEAMICIN OR LLE33288 OR LL-E33288
L7      4 S L5 AND L6
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FILE 'STNGUIDE' ENTERED AT 16:31:31 ON 15 FEB 2006

FILE 'PCTFULL' ENTERED AT 16:34:24 ON 15 FEB 2006

FILE 'STNGUIDE' ENTERED AT 16:34:50 ON 15 FEB 2006

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L8      0 S L3 AND CD27
L9      0 S L1
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FILE 'MEDLINE, BIOSIS, EMBASE, CAPLUS, TOXCENTER, DISSABS, PCTFULL'
ENTERED AT 16:37:02 ON 15 FEB 2006

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L10     439 S L5 AND CD27
L11     3 S L5 AND KI24
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FILE 'STNGUIDE' ENTERED AT 16:38:26 ON 15 FEB 2006

=> FIL MEDLINE BIOSIS EMBASE CAPLUS TOXCENTER CANCERLIT DISSABS PCTFULL
'CANCERLIT' IS NOT A VALID FILE NAME

Enter "HELP FILE NAMES" at an arrow prompt (=>) for a list of files
that are available. If you have requested multiple files, you can
specify a corrected file name or you can enter "IGNORE" to continue
accessing the remaining file names entered.

ENTER A FILE NAME OR (IGNORE):ignore

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	0.12	62.46

FILE 'MEDLINE' ENTERED AT 16:39:26 ON 15 FEB 2006

FILE 'BIOSIS' ENTERED AT 16:39:26 ON 15 FEB 2006
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=> dis his

(FILE 'HOME' ENTERED AT 16:25:49 ON 15 FEB 2006)

FILE 'MEDLINE, BIOSIS, EMBASE, CAPLUS, TOXCENTER, DISSABS, PCTFULL'
ENTERED AT 16:26:14 ON 15 FEB 2006

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L1      1932 S CD70 OR CD27L OR CD27LG OR KI24 OR KI-24 OR ANTI-CD70
L2      1360872 S TOXOID OR TOXIN OR CYTOTOXIN OR APOPTOSIS OR "CELL DEATH"
L3      839 S L1 AND L2
```

L4 762 DUP REMOVE L3 (77 DUPLICATES REMOVED)
L5 513 S L4 AND PY<=2002
L6 2709 S CALICHEAMICIN OR LLE33288 OR LL-E33288
L7 4 S L5 AND L6

FILE 'STNGUIDE' ENTERED AT 16:31:31 ON 15 FEB 2006

FILE 'PCTFULL' ENTERED AT 16:34:24 ON 15 FEB 2006

FILE 'STNGUIDE' ENTERED AT 16:34:50 ON 15 FEB 2006

L8 0 S L3 AND CD27
L9 0 S L1

FILE 'MEDLINE, BIOSIS, EMBASE, CAPLUS, TOXCENTER, DISSABS, PCTFULL'
ENTERED AT 16:37:02 ON 15 FEB 2006

L10 439 S L5 AND CD27
L11 3 S L5 AND KI24

FILE 'STNGUIDE' ENTERED AT 16:38:26 ON 15 FEB 2006

FILE 'MEDLINE, BIOSIS, EMBASE, CAPLUS, TOXCENTER, DISSABS, PCTFULL'
ENTERED AT 16:39:26 ON 15 FEB 2006

=> s L5 and CD27 and Ki24
L12 2 L5 AND CD27 AND KI24

=> dis L12 1-2 kwic

L12 ANSWER 1 OF 2 PCTFULL COPYRIGHT 2006 Univentio on STN
PI ***WO 2002094999 A2 20021128***

DETD . . . 2+ plays a pivotal role in various cell functions, ranging from
exocytosis and contraction to gene expression and cell differentiation,
proliferation
and ***apoptosis*** . Human mutations in the genes involved in
intracellular Ca²⁺ handling
result in visual defects, diabetes mellitus, disorders in the skin, . .
. .
of a cell in multicellular organisms often requires choosing between
life and death. This process of cell suicide, known as programmed
cell ***death*** or
apoptosis , occurs during a number of events in an organisms
life cycle, such as for
example, in development of an embryo, during. . . an immunological
response, or in the demise of cancerous cells after drug treatment,
among others. The
final outcome of cell survival versus ***apoptosis*** is dependent
on the balance of two
counteracting events, the onset and speed of caspase cascade activation
(essentially a
protease chain reaction), . . .
. .
controlled by the transcriptional
factor complex NF-kB. For example, exposure of cells to the protein
tumor necrosis
factor (TNF) can signal both ***cell*** ***death*** and
survival, an event playing a major role in
the regulation of immunological and inflammatory responses (Ghosh, S.,
May, M. J.,
Kopp, . . .
. .
or indirectly, treating,
preventing, diagnosing, and/or prognosing susceptibility to the
following, non-
limiting, gastrointestinal infections: Salmonella infection, E.coli
infection, E.coli
0157:H7 infection, Shiga ***Toxin*** -producing E.coli infection,
Campylobacter infection
(e.g., Campylobacter fetus, Campylobacter upsaliensis, Campylobacter
hyointestinalis, Campylobacter lari, Campylobacter jejuni, Campylobacter
concisus,
Campylobacter mucosalis, Campylobacter sputorum, Campylobacter. . .
. .
herein, transient receptor potential channel family

members have been implicated in modulating cell proliferation, differentiation, migration, activation, exocytosis, muscle contraction, gene expression, ***apoptosis*** .

present invention, including agonists and/or fragments thereof, have uses that include, modulating cell proliferation, differentiation, migration, activation, exocytosis, muscle contraction, gene expression, ***apoptosis*** . signalling, pheromone sensory signaling, smooth muscle tone, pain perception, heat perception, osmosensitivity, and mechanosensitivity.

be involved in intracellular Ca²⁺ homeostasis which affects various aspects of biological functions including mechano-regulation, pain transduction, vasorelaxation, gene expression, cell cycle and proliferation/ ***apoptosis*** . Since TRP-PLIK2 is dominantly expressed in bone marrow, it may particularly play an important role in regulating cytosolic Ca²⁺ in.

MI-MI46, MI-TI45, MI-FI44, MI-NI43] MI-Q1421 MI-11419 MI-GI40, MI-GI39, MI-HI38, MIN137, MI-SI36, MI-1135, MIN134, MI-L133] MI-KI32, MI-PI31, MI-LI30, MI-EI29, MI-MI28, MI-KI27, MI-WI.26, MI-EI25, MI- ***KI24*** , MI-LI23, MI-MI22, MI-LI21, MI-HI20, MI-LI19, MI-L118, MI-HI17, MI-DI16, MI-LI15, MI-KII4, MI-TI13, MI-DI12, MI-Y111, MI-S]IO.MI-T]09,MI-RIO8,MI-1107,M]-YI06,MI-KI05,MI-AI04,MI-HI031-MI-HI02, MI-TI01, MI-11100, MI-E99, MI-G98, MI-1)97] MI-Q969 MI-F951.

or indirectly, treating, preventing, diagnosing, and/or prognosing susceptibility to the following, non-limiting, gastrointestinal infections: Salmonella infection, E.coli infection, E.coli 0157:117 infection, Shiga ***Toxin*** -producing Ecoli infection, Campylobacter infection (e.g., Campylobacter fetus, Campylobacter upsaliensis, Campylobacter hyointestinalis, Campylobacter lari, Campylobacter jejuni, Campylobacter concisus, Campylobacter mucosalis, Campylobacter sputorum, Campylobacter rectus, Campylobacter.

herein, transient receptor potential channel family members have been implicated in modulating cell proliferation, differentiation, migration, activation, exocytosis, muscle contraction, gene expression, ***apoptosis*** .

present invention, including agonists and/or fragments thereof, have uses that include, modulating cell proliferation, differentiation, migration, activation, exocytosis, muscle contraction, gene expression, ***apoptosis*** . signalling, pheromone sensory signaling, smooth muscle tone, pain perception, heat perception, osmosensitivity, and mechanosensitivity.

involved in intracellular Ca²⁺ homeostasis which affects various aspects of biological functions including mechano-regulation, pain transduction, vasorelaxation, gene expression, cell cycle and proliferation/ ***apoptosis*** . Since TRP-PLIK2 is dominantly expressed in bone marrow, the TRP-PLIK2b splice variant may play an important role in regulating cytosolic Ca²⁺.

herein, transient receptor potential channel family members have been implicated in modulating cell proliferation, differentiation, migration, activation, exocytosis, muscle contraction, gene expression,

apoptosis .

present invention, including agonists and/or fragments thereof, have uses that include, modulating cell proliferation, differentiation, migration, activation, exocytosis, muscle contraction, gene expression, ***apoptosis*** . signalling, pheromone sensory signaling, smooth muscle tone, pain perception, heat perception, osmosensitivity, and mechanosensitivity.

be involved in intracellular Ca^{2+} homeostasis which affects various aspects of biological functions including mechano-regulation, pain transduction, vasorelaxation, gene expression, cell cycle and proliferation/ ***apoptosis*** . Since TRP-PLIK2 is dominantly expressed in bone marrow, the TRP-PLIK2c splice variant may play an important role in regulating cytosolic Ca^{2+} .

herein, transient receptor potential channel family members have been implicated in modulating cell proliferation, differentiation, migration, activation, exocytosis, muscle contraction, gene expression, ***apoptosis*** .

present invention, including agonists and/or fragments thereof, have uses that include, modulating cell proliferation, differentiation, migration, activation, exocytosis, muscle contraction, gene expression, ***apoptosis*** . signalling, pheromone sensory signaling, smooth muscle tone, pain perception, heat perception, osmosensitivity, and mechanosensitivity.

involved in intracellular Ca^{2+} homeostasis which affects various aspects of biological functions including mechano-regulation, pain transduction, vasorelaxation, gene expression, cell cycle and proliferation/ ***apoptosis*** . Since TRP-PLIK2 is dominantly expressed in bone marrow, the TRP-PLIK2d splice variant may play an important role in regulating cytosolic Ca^{2+} .

anti-peptide antibody titer may be boosted by coupling the peptide to a macromolecular carrier, such as keyhole limpet hemacyanin (KLH) or tetanus

toxoid . For instance, peptides containing cysteine residues may be coupled to a carrier using a linker such as maleimidobenzoyl- N-hydroxysuccinimide ester (MBS),.

Further, an antibody or fragment thereof may be conjugated to a therapeutic moiety such as a ***cytotoxin*** , e.g., a cytostatic or cytotoxic agent, a therapeutic agent or a radioactive metal ion, e.g., alpha-emitters such as, for example, ^{213}Bi . A ***cytotoxin*** or cytotoxic agent includes any agent that is detrimental to cells. Examples include paclitaxol, cytochalasin B, gramicidin D, ethidium bromide, emetine, mitomycin, etoposide,.

example, the drug moiety may be a protein or polypeptide possessing a desired biological activity. Such proteins may include, for example, a ***toxin*** such as abrin, ricin A, pseudomonas exotoxin, or diphtheria ***toxin*** ; a protein such as tumor necrosis factor, alpha-interferon, beta-interferon, nerve growth factor, platelet derived growth factor, tissue plasminogen activator, an apoptotic agent,.

yet to be determined, toxins, such as ricin, saporin (Mashiba H, et al., Ann. N. Y. Acad. Sci. 1999;886:233-5), or HC ***toxin*** (Tonukari NJ, et al., Plant Cell. 2000 Feb; 12(2):237-248), for example. Such fusions could be used to deliver the toxins to. . .

the fusion of antibodies directed against polypeptides of the present invention, including variants and fragments thereof, to said toxins for delivering the ***toxin*** to specific locations in a cell, to specific tissues, and/or to specific species. Such bifunctional antibodies are known in the art, . . . in addition to the references cited therein, are hereby incorporated by reference in their entirety herein. In this context, the term ***toxin*** may be expanded to include any heterologous protein, a small molecule, radionucleotides, cytotoxic drugs, liposomes, adhesion molecules, glycoproteins, ligands, cell or tissue-specific. . . antibodies, polyclonal antibodies and genetic material. In view of the present disclosure, one skilled in the art could determine whether any particular ***toxin*** could be used in the compounds of the present invention. Examples of suitable toxins listed above are exemplary only and are not. . .

protein fusions, of the present invention, or fragments thereof may be useful in inhibiting proliferative cells or tissues through the induction of ***apoptosis***. Said polypeptides may act either directly, or indirectly to induce ***apoptosis*** of proliferative cells and tissues, for example in the activation of a death-domain receptor, such as tumor necrosis factor (TNF) receptor-], CD95 (Fas/APO- 1), TNF-receptor-related ***apoptosis*** -mediated protein (TRAMP) and TNF-related ***apoptosis*** -inducing ligand (TRAIL) receptor-I and -2 (See Schulze-Osthoff K, et al., Eur J Biochem 254(3):439-59 (1998), which is hereby incorporated by reference).

Moreover, in another preferred embodiment of the present invention, said polypeptides may induce ***apoptosis*** through other mechanisms, such as in the activation of other proteins which will activate ***apoptosis***, or through stimulating the expression of said proteins, either alone or in combination with small molecule drugs or adjuvants, such as apoptonin, . . .

Diseases at the Cellular Level

Diseases associated with increased cell survival or the inhibition of ***apoptosis*** that could be treated, prevented, and/or diagnosed by the polynucleotides or polypeptides and/or antagonists or agonists of the invention, include cancers (such. . .

Diseases associated with increased ***apoptosis*** that could be treated, prevented, and/or diagnosed by the polynucleotides or polypeptides, and/or agonists or antagonists of the invention, include AIDS; neurodegenerative. . . myocardial infarction, stroke and reperfusion injury), liver injury (e.g., hepatitis related liver injury, ischemia/reperfusion injury, cholestasis (bile duct injury) and liver cancer); ***toxin*** -induced liver disease (such as that caused by alcohol), septic shock, cachexia and anorexia.

By ***toxin*** is meant compounds that bind and activate endogenous cytotoxic effector systems, radioisotopes, holotoxins, modified toxins, catalytic subunits of toxins, or any molecules. . . . antibodies (or complement fixing containing portions thereof) that bind an inherent or induced endogenous cytotoxic effector system, thymidine kinase, endonuclease, RNase, alpha ***toxin***, ricin, abrin, Pseudomonas exotoxin A, diphtheria ***toxin***, saporin, momordin, gelonin, pokeweed antiviral protein, alpha-sarcin and cholera ***toxin***. By cytotoxic prodrug is meant a non-toxic compound that is converted by an enzyme, normally present in the cell, into a cytotoxic. . . .

ID# Sequence
16520 CCUUGACAGUCUCCACACUGACAG (SEQ ID NO:310)
The TRP-PLIK2 polypeptide has been shown to be involved in the regulation of mammalian NF-KB and ***apoptosis*** pathways. Subjecting cells with an effective amount of the above antisense oligonucleotide resulted in a significant increase in IkBa expression/activity providing convincing. . . .

desired 5' end using a primer specific to the ligated RNA oligonucleotide and a primer specific to the known sequence of the ***apoptosis*** related of interest. The resultant product is then sequenced and analyzed to confirm that the 5' end sequence belongs to the relevant ***apoptosis*** related.

are not limited to, soluble forms of TNF-alpha, lymphotoxin-alpha (LT-alpha, also known as TNF-beta), LT-beta (found in complex heterotrimer LT-alpha2-beta), OPGL, FasL, ***CD27L***, CD30L, CD40L, 4-IBBL, DcR3, OX40L, TNF-gamma (International Publication No. WO 96/14328), AIN4-1 (International Publication No. CD 1 54, ***CD70***, and CD 1 53.

One of the best studied classes of B-cell co-stimulatory proteins is the TNF-superfamily. Within this family CD40, ***CD27***, and CD30 along with their respective ligands CD154, ***CD70***, and CD153 have been found to regulate a variety of immune responses. Assays which allow for the detection and/or observation of.

peripheral blood monocytes progressively lose viability when cultured in absence of serum or other stimuli. Their death results from internally regulated process (***apoptosis***). Addition to the culture of activating factors, such as TNF-alpha dramatically improves cell survival and prevents DNA fragmentation. Propidium iodide (PI) staining is used to measure ***apoptosis*** as follows.

CLMEN. . . . renal failure, proliferative disorders, cancers, ischemia-reperfusion injury, heart failure, immuno compromised conditions, HIV infection, disorders associated with aberrant NFkB regulation, disorders associated with aberrant ***apoptosis*** regulation, disorders in which decreasing NFkB activity would be therapeutically desirable, disorders in which increasing NFkB activity would be therapeutically desirable, disorders in. . . .

DETD . . . described in both plants
 and animals that are involved in pathogen perception, MHC class II
 trans-activation ,
 inflammation and the regulation of ***apoptosis*** (Inohara, N.,
 Nunez, G, ***Cell*** , ***Death*** ,
 Differ., 6(9):823-4, (1999); Inohara, N., Koseki, T., -del, Pe-so, L.,
 Hu, Y., Yee, C.,
 Chen, S., Carrio, R., Merino, J., Liu, D., Ni, J., Nunez, G, J. Biol,
 Chem. 21.,
 274(21):14560-7, (1999); Inohara, N., Nunez, G, ***Cell*** ,
 Death , Differ., 7(5):509-10,
 (2000); Harton, JA., Ting, JP, Mol, Cell, Biol., 20(17):6185-94, (2000);
 Dixon, J.,
 Brakebusch, C., Fassler, R., Dixon, MJ. Hum, Mol,. . .

Such LRRs, being extracellular, are capable of directing protein-protein
 interactions with other receptors involved in ***apoptosis*** ,
 inflammation and immune
 responses. LLR containing proteins may also bind other extracellular
 ligands derived
 from infectious agents and participate in the triggering and or
 modulating immune
 responses, particularly ***apoptosis*** .

The mechanisms that mediate ***apoptosis*** have been intensively
 studied. These
 mechanisms involve the activation of endogenous proteases, loss of
 mitochondrial
 function, and structural changes such as disruption. . .

The various signals that trigger ***apoptosis*** are thought to
 bring about these
 events by converging on a common ***cell*** ***death*** pathway,
 the core components of which
 are highly conserved from wonns, such as C. elegans, to humans. In fact,
 invertebrate
 model systems have been invaluable tools in identifying and
 characterizing the genes
 that control ***apoptosis*** . Despite this conservation of certain
 core components, apoptotic
 signaling in mammals is much more complex than in invertebrates. For
 example, in

4
 mammals there are multiple homologues of the core components in the
 cell ***death***
 signaling pathway.

. . .
 to the apoptotic program, are responsible
 for the degradation of cellular proteins that leads to the morphological
 changes seen in
 cells undergoing ***apoptosis*** . Caspases (cysteiny
 aspartate-specific proteinases) are
 cysteine proteases having specificity for aspartate at the substrate
 cleavage site.

. . .
 interaction domains, the death domain, the death effector
 domain and the caspase recruitment domain (CARD), have been identified
 within
 proteins involved in ***apoptosis*** . A fourth protein-protein
 interaction domain, the death
 recruiting domain (DRD) was recently identified in murine FLASH (Imai et
 al. (I 999)
 Nature. . .

Caspases comprise a multi-gene family having at least 12 distinct family
 members (Nicholson (1999) ***Cell*** ***Death*** and
 Differentiation 6: 1028). A relatively
 small fraction of cellular polypeptides (less than 200) are thought to
 serve as targets
 for cleavage. . . these caspase targets perforin key cellular
 functions, their proteolysis is thought to account for the cellular and
 morphological

events that occur during ***apoptosis*** . Members of the caspase gene family can be divided by phylogenetic analysis into two major subfamilies, based upon their relatedness to ICE. . .

SEQ ID NO:2 or

35, in addition to, its encoding nucleic acid, wherein the medical condition is a disorder related to aberrant ***apoptosis*** modulation, either directly or indirectly.

and/or fragments thereof, have uses that include detecting, prognosing, treating, preventing, and/or ameliorating the following diseases and/or disorders, disorders related to aberrant ***apoptosis*** regulation, disorders related to aberrant cell adhesion regulation, and disorders related to aberrant cellular proliferation, for example, in addition to, neural, immune,. . .

M1-I,146, M1-RI45, M1-NI44, MI-DI43, M1-F142, M1-LI41, M1-E140, MI-LI39, MI-TI38, M1-NI37, MI-L136, MI-SI35, MI-PI34, MI-LI33, MI-G132, MI-N131, MI-F130, M1-A129, M1-G128] M1-VI27, MI-E126, M1-1125, MI- ***KI24*** , M1-R123, M1-VI22, MI-L121, MI-N120]M1-K119]MI-S118]M1-LI17]MI-QI16]MI-LI155MI-1114]MI-E113] MI-I,112, M1-H111, M1-RHO, MI-1,109, MI-HI08, MI-KI07, MI-F106, M1-50 T105] MI-D104, MIJ103, M1-R102, M1-1101, MIN10% M1-Q99] M1-198] M1-G979 M1-N96, M1-E953. . .

anti-peptide antibody titer may be boosted by coupling the peptide to a macromolecular carrier, such as keyhole limpet hemacyanin (KLH) or tetanus

toxoid . For instance, peptides containing cysteine residues may be coupled to a carrier using a linker such as maleimidobenzoyl- N-hydroxysuccinimide ester (MBS),. . .

117

Further, an antibody or fragment thereof may be conjugated to a therapeutic moiety such as a ***cytotoxin*** , e.g., a cytostatic or cytotoxic agent, a therapeutic agent or a radioactive metal ion, e.g., alpha-emitters such as, for example, ²¹³Bi. A ***cytotoxin*** or cytotoxic agent includes any agent that is detrimental to cells. Examples include paclitaxol, cytochalasin B, gramicidin D, ethidium bromide, emetine, mitomycin, etoposide,. . .

example, the drug moiety may be a protein or polypeptide possessing a desired biological activity. Such proteins may include, for example, a ***toxin*** such as abrin, ricin A, pseudomonas exotoxin, or diphtheria ***toxin*** ; a protein such as tumor necrosis factor, alpha-interferon, beta-interferon, nerve growth factor, platelet derived growth factor, tissue plasminogen activator, an apoptotic agent,. . .

Detection And Therapy, Baldwin et al. (eds.), pp. 303-16 (Academic Press 1985), and Thorpe et al., The Preparation And Cytotoxic Properties Of Antibody- ***Toxin*** Conjugates, Immunol. Rev. 62:119-58 (1982).

yet to be determined, toxins, such as ricin, saporin (Mashiba H, et al., Ann. N. Y. Acad. Sci. 1999;886:233-5), or HC ***toxin*** (Tonukari NJ, et al., Plant Cell. 2000 Feb;12(2):237-248), for

example. Such fusions could be used to deliver the toxins to desired. .

.
the fusion of antibodies directed against polypeptides of the present invention, including variants and fragments thereof, to said toxins for delivering the ***toxin*** to specific locations in a cell, to specific tissues, and/or to specific species. Such bifunctional antibodies are known in the art, . . . in addition to the references cited therein, are hereby incorporated by reference in their entirety herein. In this context, the term ***toxin*** may be expanded to include any heterologous protein, a small molecule, radionucleotides, cytotoxic drugs, liposomes, adhesion molecules, glycoproteins, ligands, cell or tissue-specific. . . antibodies, polyclonal antibodies and genetic material. In view of the present disclosure, one skilled in the art could determine whether any particular ***toxin*** could be used in the compounds of the present invention. Examples of suitable toxins listed above are exemplary only and are not. . .

.
protein fusions, of the present invention, or fragments thereof may be useful in inhibiting proliferative cells or tissues through the induction of ***apoptosis***. Said polypeptides may act either directly, or indirectly to induce ***apoptosis*** of proliferative cells and tissues, for example in the activation of a death-domain receptor, such as tumor necrosis factor (TNF) receptor- 1, CD95 (Fas/APO- 1), TNF-receptor-related ***apoptosis*** -mediated protein (TRAMP) and TNIT-related ***apoptosis*** -inducing ligand (TRAIL) receptor-1 and -2 (See Schulze-Osthoff K, et al., Eur J Biochem. 254(3):439-59 (1998), which is hereby incorporated by reference).

Moreover, in another preferred embodiment of the present invention, said polypeptides may induce ***apoptosis*** through other mechanisms, such as in the activation of other proteins which will activate ***apoptosis***, or through stimulating the expression of said proteins, either alone or in combination with small molecule drugs or adjuvants, such as apoptonin, . . .

Diseases at the Cellular Level

Diseases associated with increased cell survival or the inhibition of ***apoptosis*** that could be treated, prevented, and/or diagnosed by the polynucleotides or polypeptides and/or antagonists or agonists of the invention, include cancers (such. . .

Diseases associated with increased ***apoptosis*** that could be treated, prevented, and/or diagnosed by the polynucleotides or polypeptides, and/or agonists or antagonists of the invention, include AIDS; neurodegenerative. . . by myocardial infarction, stroke and reperfusion injury), liver injury (e.g., hepatitis related liver injury, ischemia/reperfusion injury, cholestasis (bile duct injury) and liver cancer); ***toxin*** -induced liver disease (such as that caused by alcohol), septic shock, cachexia and anorexia.

.
and/or diagnosed according to the invention include, but are not limited to, diseases, disorders, and/or conditions such as infarction, infection, exposure to ***toxin***, trauma, surgical damage,

degenerative disease or malignancy that may affect motor neurons as well as other components of the nervous system, as. . .

antibodies (or complement fixing containing portions thereof) that bind an inherent or induced endogenous cytotoxic effector system, thymidine kinase, endonuclease, RNase, alpha ***toxin***, ricin, abrin, Pseudomonas exotoxin A, diphtheria ***toxin***, saporin, momordin, gelonin, pokeweed antiviral protein, alpha-sarcin and cholera ***toxin***. By cytotoxic prodrug is meant a non-toxic compound that is converted by an enzyme, normally present in the cell, into a cytotoxic. . .

Bertin, J., and DiStefano, P. S. (2000). The PYRIN Domain: A novel Motif found in

apoptosis and inflammation proteins. ***Cell***
Death Differ. In press.

morphogenesis and has striking similarities to Toll. Development 120, 885
Gavrieli, Y., Sherman, Y., and Ben-Sasson, S. A. (1992). Identification of programmed ***cell*** ***death*** in situ via specific labeling of nuclear DNA fragmentation. J.

256

Example 6 - Method Of Assessing The Ability Of HLRRNSI To Modulate
Apoptosis .

The role of the novel HLRRNSI polypeptides in either promoting or inhibiting ***apoptosis*** could be determined by the generation of transfected cell lines with the HLRRNSI polynucleotides of the present invention, either transient or stable, . . . by reference in its entirety) which involves end labeling broken ends of double-stranded DNA with biotin-conjugated dUTP using terminal transferase. Cells undergoing ***cell*** ***death*** can then be easily detected by staining with FITC-conjugated streptavidin and flow cytometric quantitation.

in the mitotic index where HLRRNS1 stimulates cell proliferation indicates apoptotic activity. Likewise, a decrease in cell numbers where HLRRNS I stimulates ***apoptosis*** indicates apoptotic activity.

the cells and other cellular properties. FCM detects and quantifies the uptake of fluorescent molecules that diagnose events preceding or coincident with ***cell*** ***death***. These events include changes in nuclear DNA content as measured by staining of DNA with propidium iodide; changes in cell size.

desired 5' end using a primer specific to the ligated RNA oligonucleotide and a primer specific to the known sequence of the ***apoptosis*** related of interest. The resultant product is then sequenced and analyzed to confirm that the 5' end sequence belongs to the relevant ***apoptosis*** related.

are not limited to, soluble forms of TNF-alpha, lymphotoxin-alpha (LT-alpha, also known as TNF-beta), LT-beta (found in complex heterotrimer LT-alpha2-beta), OPGL, FasL, ***CD27L***, CD30L, CD40L, 4-IBBL, DcR3, OX40L,

TNF-gamma

301

(International Publication No. WO 96/14328), AIM-I (International Publication No.

One of the best studied classes of B-cell co-stimulatory proteins is the TNF-superfamily. Within this family CD40, ***CD27***, and CD30 along with their respective ligands CD 154, ***CD70***, and CD 153 have been found to regulate a variety of immune responses. Assays which allow for the detection and/or observation.

peripheral blood monocytes progressively lose viability when cultured in absence of serum or other stimuli. Their death results from internally regulated process (***apoptosis***). Addition to the culture of activating factors, such as TNF-alpha dramatically improves cell survival and prevents DNA fragmentation. Propidium iodide (PI) staining is used to measure ***apoptosis*** as follows.

CLMEN. . . method for preventing, treating, or ameliorating a medical condition of claim I 1, wherein the medical condition is disorder related to aberrant ***apoptosis*** modulation, either directly or indirectly.

361

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(FILE 'HOME' ENTERED AT 16:25:49 ON 15 FEB 2006)

FILE 'MEDLINE, BIOSIS, EMBASE, CAPLUS, TOXCENTER, DISSABS, PCTFULL' ENTERED AT 16:26:14 ON 15 FEB 2006

L1 1932 S CD70 OR CD27L OR CD27LG OR KI24 OR KI-24 OR ANTI-CD70
L2 1360872 S TOXOID OR TOXIN OR CYTOTOXIN OR APOPTOSIS OR "CELL DEATH"
L3 839 S L1 AND L2
L4 762 DUP REMOVE L3 (77 DUPLICATES REMOVED)
L5 513 S L4 AND PY<=2002
L6 2709 S CALICHEAMICIN OR LLE33288 OR LL-E33288
L7 4 S L5 AND L6

FILE 'STNGUIDE' ENTERED AT 16:31:31 ON 15 FEB 2006

FILE 'PCTFULL' ENTERED AT 16:34:24 ON 15 FEB 2006

FILE 'STNGUIDE' ENTERED AT 16:34:50 ON 15 FEB 2006

L8 0 S L3 AND CD27
L9 0 S L1

FILE 'MEDLINE, BIOSIS, EMBASE, CAPLUS, TOXCENTER, DISSABS, PCTFULL' ENTERED AT 16:37:02 ON 15 FEB 2006

L10 439 S L5 AND CD27
L11 3 S L5 AND KI24

FILE 'STNGUIDE' ENTERED AT 16:38:26 ON 15 FEB 2006

FILE 'MEDLINE, BIOSIS, EMBASE, CAPLUS, TOXCENTER, DISSABS, PCTFULL' ENTERED AT 16:39:26 ON 15 FEB 2006

L12 2 S L5 AND CD27 AND KI24

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L12 ANSWER 1 OF 2 PCTFULL COPYRIGHT 2006 Univentio on STN
AN 2002094999 PCTFULL ED 20021210 EW 200248
TIEN POLYNUCLEOTIDE ENCODING A NOVEL TRP CHANNEL FAMILY MEMBER, TRP-PLIK2,
AND SPLICE VARIANTS THEREOF
TIFR POLYNUCLEOTIDE CODANT UN NOUVEAU MEMBRE DE LA FAMILLE DES CANAUX TRP,
TRP-PLIK2, ET VARIANT D'EPISSAGE DE CE POLYNUCLEOTIDE
IN LEE, Ning, 926 Rhoads Drive, Belle Mead, NJ 08807, US [US, US];
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FEDER, John, 277 Dutchtown Zion Road, Belle Mead, NJ 08502, US [US, US];

WU, Shujian, 972 Ithan Lande, Langhorne, PA 19047, US [CN, US];
 CHANG, Han, 2 Ann's Court, Princeton Junction, NJ 08550, US [US, US];
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 BLANAR, Michael, 1325 Summerhill Drive, Malvern, PA 19355, US [CA, US];
 BOL, David, 1467 Franklin Road, Langhorne, PA 19047, US [US, US]
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 FEDER, John, 277 Dutchtown Zion Road, Belle Mead, NJ 08502, US [US, US], for US only;
 WU, Shujian, 972 Ithan Lande, Langhorne, PA 19047, US [CN, US], for US only;
 CHANG, Han, 2 Ann's Court, Princeton Junction, NJ 08550, US [US, US], for US only;
 LEE, Liana, 8 Petunia Drive Apt. 1J, North Brunswick, NJ 08902, US [US, US], for US only;
 BLANAR, Michael, 1325 Summerhill Drive, Malvern, PA 19355, US [CA, US], for US only;
 BOL, David, 1467 Franklin Road, Langhorne, PA 19047, US [US, US], for US only
 AG D'AMICO, Stephen, Bristol-Myers Squibb Company, P.O. Box 4000, Route 206 and Provinceline Road, Princeton, NJ 08543-4000, US
 LAF English
 LA English
 DT Patent
 PI ***WO 2002094999 A2 20021128***
 DS W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU
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 IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN
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 RW (EPO): AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE TR
 RW (OAPI): BF BJ CF CG CI CM GA GN GQ GW ML MR NE SN TD TG
 AI WO 2002-US16164 A 20020522
 PRAI US 2001-60/292,599 20010522
 US 2002-60/362,944 20020308
 L12 ANSWER 2 OF 2 PCTFULL COPYRIGHT 2006 Univentio on STN
 AN 2002074959 PCTFULL ED 20021010 EW 200239
 TIEN A NOVEL HUMAN LEUCINE-RICH REPEAT CONTAINING PROTEIN EXPRESSED
 TIFR PREDOMINATELY IN NERVOUS SYSTEM TISSUES, HLRRNS1
 IN HLRRNS1: NOUVELLE PROTEINE HUMAINE A REPETITIONS RICHES EN LEUCINE
 EXPRIMEE ESSENTIELLEMENT DANS DES TISSUS DU SYSTEME NERVEUX
 RAMANATHAN, Chandra, 41 Alison Avenue, Wallingford, CT 06492, US;
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 MINTIER, Gabe, 318 Morrison Ave., Hightstown, NJ 08520, US
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 AG D'AMICO, Stephen, Bristol-Myers Squibb Company, P.O. Box 4000, Route 206 and Provinceline Road, Princeton, NJ 08543-4000, US
 LAF English
 LA English
 DT Patent
 PI ***WO 2002074959 A2 20020926***
 DS W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU
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 RW (EPO): AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE TR
 RW (OAPI): BF BJ CF CG CI CM GA GN GQ GW ML MR NE SN TD TG
 AI WO 2001-US50457 A 20011220
 PRAI US 2001-60/259,479 20010103
 US 2001-60/260,616 20010109

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FILE 'MEDLINE, BIOSIS, EMBASE, CAPLUS, TOXCENTER, DISSABS, PCTFULL'
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L2 1360872 S TOXOID OR TOXIN OR CYTOTOXIN OR APOPTOSIS OR "CELL DEATH"
L3 839 S L1 AND L2
L4 762 DUP REMOVE L3 (77 DUPLICATES REMOVED)
L5 513 S L4 AND PY<=2002
L6 2709 S CALICHEAMICIN OR LLE33288 OR LL-E33288
L7 4 S L5 AND L6

FILE 'STNGUIDE' ENTERED AT 16:31:31 ON 15 FEB 2006

FILE 'PCTFULL' ENTERED AT 16:34:24 ON 15 FEB 2006

FILE 'STNGUIDE' ENTERED AT 16:34:50 ON 15 FEB 2006

L8 0 S L3 AND CD27
L9 0 S L1

FILE 'MEDLINE, BIOSIS, EMBASE, CAPLUS, TOXCENTER, DISSABS, PCTFULL'
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L10 439 S L5 AND CD27
L11 3 S L5 AND KI24

FILE 'STNGUIDE' ENTERED AT 16:38:26 ON 15 FEB 2006

FILE 'MEDLINE, BIOSIS, EMBASE, CAPLUS, TOXCENTER, DISSABS, PCTFULL'
ENTERED AT 16:39:26 ON 15 FEB 2006

L12 2 S L5 AND CD27 AND KI24

=> dis L7 1-4 bib

L7 ANSWER 1 OF 4 PCTFULL COPYRIGHT 2006 Univentio on STN
AN 2002083921 PCTFULL ED 20021107 EW 200243
TIEN NULEIC ACIDS AND CORRESPONDING PROTEINS USEFUL IN THE DETECTION AND
TREATMENT OF VARIOUS CANCERS
TIFR ACIDES NUCLEIQUES ET PROTEINES CORRESPONDANTES UTILES POUR LA DETECTION
ET LE TRAITEMENT DE DIVERS CANCERS
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LAF English
LA English
DT Patent
PI ***WO 2002083921 A2 20021024***
DS W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU
CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN
IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN
MW MX MZ NO NZ OM PH PL PT RO RU SD SE SG SI SK SL TJ TM
TN TR TT TZ UA UG UZ VN YU ZA ZM ZW
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RW (EAPO): AM AZ BY KG KZ MD RU TJ TM
RW (EPO): AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE TR
RW (OAPI): BF BJ CF CG CI CM GA GN GQ GW ML MR NE SN TD TG
AI WO 2002-US11654 A 20020410
PRAI US 2001-60/283,112 20010410
US 2001-60/282,739 20010410
US 2001-60/286,630 20010425

L7 ANSWER 2 OF 4 PCTFULL COPYRIGHT 2006 Univentio on STN
AN 2002029032 PCTFULL ED 20020627 EW 200215

TIEN WHOLE CELL ENGINEERING BY MUTAGENIZING A SUBSTANTIAL PORTION OF A
 STARTING GENOME, COMBINING MUTATIONS, AND OPTIONALLY REPEATING
 TIFR MANIPULATION DE CELLULE ENTIERE PAR MUTAGENESE D'UNE PARTIE
 SUBSTANTIELLE D'UN GENOME DE DEPART, PAR COMBINAISON DE MUTATIONS ET
 EVENTUELLEMENT PAR REPETITION
 IN SHORT, Jay, M., P.O. Box 7214, Rancho Santa Fe, CA 92067-7214, US [US,
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 LAF English
 LA English
 DT Patent
 PI ***WO 2002029032 A2 20020411***
 DS W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU
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 RW (EPO): AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE TR
 RW (OAPI): BF BJ CF CG CI CM GA GN GQ GW ML MR NE SN TD TG
 AI WO 2001-US31004 A 20011001
 PRAI US 2000-09/677,584 20000930
 US 2001-60/279,702 20010328
 US 2001-PCT/US01/19367 20010614
 L7 ANSWER 3 OF 4 PCTFULL COPYRIGHT 2006 Univentio on STN
 AN 2002018620 PCTFULL ED 20020705 EW 200210
 TIEN NEUTROKINE-ALPHA AND NEUTROKINE-ALPHA SPLICE VARIANT
 TIFR NEUTROKINE-ALPHA ET VARIANT D'EPISSAGE DE NEUTROKINE-ALPHA
 IN YU, Guo-Liang, 242 Gravatt Drive, Berkeley, CA 94705, US [US, US];
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 [US, US], for US only;
 ULLRICH, Stephen, 4713 Rams Head Court, Rockville, MD 20853, US [US,
 US], for US only
 AG HOOVER, Kenley, 9410 Key West Avenue, Rockville, MD 20850, US
 LAF English
 LA English
 DT Patent
 PI ***WO 2002018620 A2 20020307***
 DS W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU
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		UA	UG	US	UZ	VN	YU	ZA	ZW												
	RW	(ARIPO):	GH	GM	KE	LS	MW	MZ	SD	SL	SZ	TZ	UG	ZW							
	RW	(EAPO):	AM	AZ	BY	KG	KZ	MD	RU	TJ	TM										
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	RW	(OAPI):	BF	BJ	CF	CG	CI	CM	GA	GN	GQ	GW	ML	MR	NE	SN	TD	TG			
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PRAI	US	2000-60/225,628																			
	US	2000-60/227,008																			
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	US	2001-60/296,122																			
	US	2001-60/304,809																			

L7 ANSWER 4 OF 4 PCTFULL COPYRIGHT 2006 Univentio on STN
AN 2001096551 PCTFULL ED 20020826
TIEN WHOLE CELL ENGINEERING BY MUTAGENIZING A SUBSTANTIAL PORTION OF A
STARTING GENOME, COMBINING MUTATIONS, AND OPTIONALLY REPEATING
TIFR INGENIERIE CELLULAIRE COMPLETE PAR MUTAGENESE D'UNE PARTIE SUBSTANTIELLE
D'UN GENOME DE DEPART, PAR COMBINAISON DE MUTATIONS ET EVENTUELLEMENT
REPETITION
IN SHORT, Jay, M.
PA DIVERSA CORPORATION;
SHORT, Jay, M.
DT Patent
PI ***WO 2001096551 A2 20011220***
DS W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU
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MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT
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UG ZW AM AZ BY KG KZ MD RU TJ TM AT BE CH CY DE DK ES FI
FR GB GR IE IT LU MC NL PT SE TR BF BJ CF CG CI CM GA GN
GW ML MR NE SN TD TG

AI	WO	2001-US19367	A	20010614
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	US	2000-09/677,584		20000930

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COST IN U.S. DOLLARS	SINCE FILE	TOTAL
	ENTRY	SESSION
FULL ESTIMATED COST	63.28	125.74

STN INTERNATIONAL LOGOFF AT 17:06:13 ON 15 FEB 2006